REMARKS

Claims 1, 3, 10-17 and 19-28 are pending in the application. Claims 10-16, 20, 24 and 26 have been withdrawn; thus claims 1, 3, 17, 19, 21-23, 25, 27 and 28 are presented for examination.

Rejection Under 35 U.S.C. §103(a)

Claims 1, 3, 17, 19, 21-23, 25, 27 and 28 have been rejected under 35 U.S.C. §103(a) over Weber, WO 2003/026532 (Weber) in view of Weber et al., US 6,743,463 (Weber II) and further in view of Tsipursky et al., US 5,998,528 (Tsipursky). This rejection is respectfully traversed.

For a proper obviousness rejection, the differences between the subject matter sought to be patented and the prior art must be such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. 35 U.S.C. §103(a). The key to supporting any rejection under 35 U.S.C. §103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. MPEP 2141. " '[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.' " *KSR International Co.* v. *Teleflex Inc.*, 550 U.S. ___, 82 USPQ2d 1385 (2007), quoting *In re Kahn ,* 441 F.3d 977, 988 (Fed. Cir. 2006). The prior art reference (or references when combined) must teach or suggest all the claimed features. "When determining whether a claim is obvious, an examiner must make 'a searching comparison of the claimed invention – *including all its limitations* – with the teaching of the prior art.' … Thus, 'obviousness requires a suggestion of all limitations in a claim.' …" *Ex parte Wada and Murphy*, BPAI Appeal No. 2007-3733, January 14, 2008 (emphasis in original) (citations omitted). In addition, there must be a reasonable expectation of success. See MPEP 2143.02.

Weber, Weber II and Tsipursky do not render the currently claimed invention unpatentable under 35 USC 103(a), which invention is directed to an implantable or insertable medical device comprising a release region, said release region comprising (a) a polymeric carrier comprising a hydrophobic first polymer and (b) drug loaded nanoparticles dispersed within said polymeric carrier, said drug loaded nanoparticles comprising: silicate particles comprising a layered silicate

material; a hydrophilic first therapeutic agent; and a hydrophilic second polymer, wherein the first therapeutic agent and hydrophilic second polymer are structurally associated with the silicate particles in that the first therapeutic agent and hydrophilic second polymer occupy spaces between adjacent layers of the silicate material of each silicate particle to form a depot for the first therapeutic agent.

In this regard, Weber at page 7, line 29 to page 8, line 15 describes the technology therein as including a matrix material as follows (emphasis added):

> . . . a matrix material according to the invention may be any material suitable, or later determined to be suitable, for use in such a medical device. The matrix ***material may be any material that is historically or currently utilized, or contemplated for future use,*** in a corresponding medical device not comprising a nanocomposite component. The matrix material ***may be comprised of organic, inorganic or hybrid organic/inorganic materials.*** Additionally, the matrix material may be a single material or a combination of materials, e.g.***, the matrix material may be a metal alloy, copolymer or polymer blend.***
>
> Exemplary matrix materials include, for example, polymers, such as thermoplastics and thermosets. Examples thermoplastics suitable for use as a matrix material include, for example polyolefins, polyamides, polyesters, polyethers, polyurethanes, polyureas, polyvinyls, ***polyacrylics,*** fluoropolymers, copolymers and block copolymers thereof, and mixtures thereof. Representative examples of thermosets that may be utilized as a matrix material include clastomers [*sic*, elastomers] such as EPDM, epichlorohydrin, nitrile butadiene elastomers, silicones, etc. Conventional thermosets such as expoxies, isocyanates, etc. , can also be used. Biocompatible thermosets may also be used and these include, for example, biodegradable polycaprolactone, poly (dimethylsiloxane) containing polyurethanes and ureas, and polysiloxanes.

The Examiner argues that this portion of Weber teaches a polymer blend and that this description can be used to meet the hydrophobic first polymer second and hydrophilic second polymer element of the claimed invention. This, however, is merely improper hindsight reconstruction, using the present invention as a roadmap.

For example, out of the myriad materials encompassed by the above, a person of ordinary skill in the art would first have to select an organic material, more particularly a polymer, even more particularly a polymer blend. Furthermore, as components of the polymer blend, that person would have to select a *combination* of a hydrophobic polymer and a hydrophilic polymer. Such a combination is not described Weber.

Moreover, there are good reasons *not* to choose such a combination, not the least of which is the fact that such materials do not ordinarily mix with one another (e.g., the classic incompatibility of hydrophobic oil and hydrophilic water).

The Examiner also argues (a) that the materials being claimed are explicitly disclosed in the reference and (b) that the selection of a known material based on its suitability for its intended use supports a *prima facie* obviousness determination (citing *Sinclair & Carroll Co. v. Interchemical Corp.*,325 U.S. 327, 65 USPQ 297 (1945) and MPEP 2144.07).

Applicant respectfully disagrees. Rather than constituting selection of a known material based on art recognized suitability for an intended use, the presently claimed invention constitutes selection of an unique *combination* of materials for a *novel* use. In this regard, the inventor has devised a novel scheme that is useful for allowing hydrophilic therapeutic agents to be incorporated into hydrophobic carrier regions (see paragraphs [0003] and [0011] of the instant specification). As a specific example, Applicant describes an embodiment of the invention in the Example (paragraphs [0081]-[0082] of the instant specification) wherein a hydrophilic drug (i.e., halofuginone) and a hydrophilic polymer (i.e., hyaluronic acid) are incorporated into silicate particles (montmorillonite clay) to provide a drug-loaded nanoparticles, which are then dispersed within a hydrophobic polymer (SIBS) carrier.

The Examiner also points to the polyacrylics recited at page 8, line 8 of Weber (see above) in support of the Examiner's allegation that Weber teaches a hydrophilic polymer for use in a polymer blend.

Polyacrylics are known, however, which are hydrophobic. In this regard, see, e.g., paragraph [0034] of U.S. Patent Pub. No. 2008/0193504: "Suitable polymers are silicone oils and elastomers cross-linked hydrophilic polymers such as naturally occurring polymers, polyurethanes, hydrophilic and ***hydrophobic polyacrylic compounds***."

In response, the Examiner urges that polymers and copolymers of acrylic and methacrylic acid and polymers and copolymers of methacrylamide are cited as examples of hydrophilic polymers at paragraph [0043] of the instant specification. Applicant's point, however, was not that there are no hydrophilic polyacrylics, but rather that polyacrylics are known which are

hydrophobic. "The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." MPEP 2112 (emphasis in original), citing *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993

In support of the argument regarding the obviousness of claim 1, the Examiner further refers page 9, line 4 of Weber, which in larger context is set forth within the paragraph at page 9, lines 3-21 of Weber (emphasis added):

> Examples of materials suitable for use in the nanoparticles include, among others, ***synthetic or natural smectic phyllosilicates including clays and micas (that may optionally be*** intercalated, ***exfoliated*** and/or otherwise chemically modified) such as montmorillonite (mmt), hectorites, hydrotalcites, vermiculite, and laponite; monomeric silicates such as polyhedral oligomeric silsequioxanes (POSS) including various functionalized POSS and polymerized POSS; carbon and ceramic nano- tubes, nano-wires and nano-fibers, including carbon nanofibers and nanotubes of any geometry prepared by electrospinning a carbonizable material, such as polyacrylonitrile; single and multi-walled fullerene nanotubes, silica nanogels, and alumina nano-fibers, as well as metal and metal oxide powders including aluminum oxide (AlO_3), titanium oxide (TiO_2), tungsten oxide, zirconium oxide, gold (Au), silver (Ag), platinum (Pt) and magnetic or paramagnetic materials such as neodinium iron boron or super paramagnetic ferrite oxide (Fe_3O_4) or super paramagnetic maghemite (Fe_2O_3); organic materials including temperature sensitive polymers, such as polyvinylpyrrolidone and n-isopropylacrylamide copolymers or blends, and poloxamer, biodegradable polymers such as poly (lactic) acid, polysaccharide, polyalkylcyanoacrylate, which biodegradable polymers may also be magnetized; and further including polytetrafluoroethylene, and dendrimers or dendrimer metal complexes.

To arrive at the claimed invention, one of ordinary skill in the art would have, among other things, to choose smectic phyllosilicates over all the other diverse materials listed, and that person would have to further choose to intercalate the thus-selected phyllosilicates, rather than exfoliate them as taught by Weber.

This selection is coupled with the fact that a person of ordinary skill in the art would also have to select an organic material, more particularly a polymer, even more particularly a polymer blend from the materials in Weber, and that as components of the polymer blend, that person would have to select a combination of a hydrophobic polymer and a hydrophilic polymer (see above).

Weber II, which is cited for its teaching regarding halofuginone, does not cure the above-noted deficiencies in Weber. For example, it was previously argued that Weber II does not appear

to describe, in combination, a hydrophilic polymer and a hydrophobic polymer and, in fact, Weber II does not appear to describe polymer blends at all. It was also argued that Weber II appears to describe intercalated layered silicate particles.

In response to this argument, the Examiner states that Weber (rather than Weber II) was invoked for the teaching of a hydrophilic polymer and a hydrophobic polymer combination. The Examiner further argues, however, that Weber II also teaches hydrophobic polymers such as polyurethanes (see col. 9, lines 31-60) and hydrophilic polymers such as albumin (see col. 13, line 2). It is noted, however, that Weber II teaches the use of albumin as a biologically active material (rather than a polymer in a polymer blend) and that Weber II does not appear to describe the *combination* of albumin (which the Examiner is characterizing as a hydrophilic polymer) *and* another therapeutic agent (specifically a hydrophilic therapeutic agent such as halofuginone) *and* a hydrophobic polymer.

Finally, the Examiner notes that Weber and Webber II do not explicitly disclose the placement of the therapeutic agent in the spaces between adjacent layers of the silicate material of each silicate particle to form a depot, but argues that the placement of a hydrophilic therapeutic agent and a hydrophilic polymer in the spaces between the adjacent layers of the silicate material is a property of interaction between the silicate and the hydrophilic therapeutic agent and polymer. In support, the Examiner refers to col. 5, lines 9-19 of Tsipursky, but quotes the text found at col. 4, lines 40-54 of Tsipursky, which in more meaningful context is set forth within the paragraph at col. 4, lines 40-54 of Tsipursky (emphasis added):

> In accordance with an important feature of the present invention, it has been found that the ***addition of metal cations***, preferably during intercalation and/or exfoliation, or ***the addition of metal cations*** to a nanocomposite composition of an organic liquid and an intercalate or exfoliate thereof, unexpectedly increases the viscosity of an ***organic liquid-containing nanocomposite composition***. It is preferred that the ***metal cation has a valence of at least 2, more preferably at least 3***, although monovalent salts (preferably not NaOH) also increase the viscosity to a lesser degree. The ***anion portion of the cation-containing compound, added to provide cations***, may be inorganic or organic and the ***cation-containing compound*** is added in solution (with water and/or an organic solvent) ***to provide metal cations, as well as anions, in solution***. The addition of the metal cations in solution to the intercalating composition ***results in sufficient intercalation for easy exfoliation using less intercalant***. It is theorized that ***polar moieties from the intercalant molecules***, which complex to the ***interlayer cations in the interlayer spaces between the platelets of the layered material***, also complex with the added cations, and the complexed metal salt-

> derived cations carry their dissociated anions along with the cations, in the interlayer space, in order to maintain charge neutrality within the interlayer spaces of the layered material. It is theorized that such double intercalant complexing (intercalant with interlayer cations and with cations from the added metal salt compound) occurs on adjacent, opposed platelet surfaces, resulting in repulsion between closely spaced dissociated anions carried by the added cations, resulting in increased basal spacing and more complete exfoliation using less intercalant.

The system in Tsipursky, however, is designed for exfoliation, which would destroy the limitation of claim 1 wherein the first therapeutic agent and the hydrophilic second polymer are structurally associated with the silicate particles in that the first therapeutic agent and hydrophilic second polymer occupy spaces between adjacent layers of the silicate material of each silicate particle to form a depot for the first therapeutic agent.

Moreover, the system described in Tsipursky includes, *inter alia*, (a) an organic liquid, (b) a layered material with interlayer cations in the interlayer spaces between the platelets of the layered material, (b) intercalant molecules with polar moieties and (c) a cation-containing compound which provides metal cations and associated anions.

This system is unrelated to the system proposed by the Examiner on the basis of Weber and Weber II, for example, because the system proposed by the Examiner does not include intercalant molecules with polar moieties *and* a cation-containing compound which provides *metal cations and associated anions*. Note also that the system described in Tsipursky does not comprise a hydrophobic polymer. Moreover, as noted above, the system described in Tsipursky leads to exfoliation.

A better understanding of the claimed invention and its differences from the prior art may be obtained from one specific embodiment of the invention described in the Example at paragraphs [0081]-[0082] of the instant specification, in which a scheme is described wherein a hydrophilic therapeutic agent is incorporated into hydrophobic carrier regions. As noted at paragraph [0003] of the instant specification, where the drug is hydrophilic and the polymer is hydrophobic, attempts to blend the drug into the polymer commonly result in unstable formulations with accompanying phase separation.

More specifically, in the Example, silicate particles (i.e., montmorillonite clay) are added to an aqueous solution comprising a hydrophilic therapeutic agent (i.e., halofuginone) and a

hydrophilic polymer (hyaluronic acid), after which the combination is dried and ground as needed, thereby providing a drug-loaded nanoparticle powder in which the hydrophilic therapeutic agent and the hydrophilic polymer occupy spaces between adjacent layers of the silicate material of the silicate particles. (As noted in the Example, and in contrast to Tsipursky, the nanoclay is not exfoliated into individual platelets prior to freeze-drying and grinding.) The drug-loaded nanoparticles are subsequently added to a solution of a hydrophobic polymer (i.e., SIBS) in an organic solvent (i.e., toluene), forming a stable suspension, which is then used to form a layer of drug-loaded nanoparticles dispersed within a hydrophobic polymer (i.e., SIBS) carrier.

For at least the preceding reasons, claim 1, and claims 3, 17, 19, 21-23, 25, 27 and 28 depending therefrom are patentable over Weber, Weber II and Tsipursky.

Conclusion

Applicants submit that all pending claims are in condition for allowance. Reconsideration is requested and an early notice of allowance is earnestly solicited. The Examiner is invited to telephone the Applicant's attorney at the number listed below in order to resolve any outstanding issues in this case.

Respectfully submitted,

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